ABSTRACT

Short peptides containing $C^{\alpha,\alpha}$-dipropylglycine (Dpg) at alternating sequence positions were synthesized and examined for conformational behavior. Peptide assembly was performed using Fmoc-solid-phase chemistry where the coupling with PyAOP could be significantly enhanced at elevated temperature. Circular dichroism (CD) and NMR conformational studies revealed that incorporation of Dpg residues induced folded structures into peptides. It was observed that Dpg residues adopted helical conformation in a helix-promoting sequence. The resulting helical structure was comprised of consecutive β-turns whose structure was stabilized by salt bridge in aqueous solution.

In this study, the preparation of sterically and polyfunctional $C^{\alpha,\alpha}$-disubstituted amino acids (ααAAs) via alkylation of ethyl nitroacetate and transformation into derivatives ready for incorporation into peptides are described. Treatment of ethyl nitroacetate with N,N-diisopropylethylamine in the presence of a catalytic amount of tetraalkylammonium salt, followed by the addition of an activated alkyl halide or Michael acceptor, gave the doubly C-alkylated product in good to excellent yields. Selective nitro reduction with Zn in acetic or hydrogen over Raney Ni gave the corresponding amino ester that, upon saponification, can be protected with the fluorenylmethyloxycarbonyl (Fmoc) group. The synthesis of a sterically demanding $C^{\alpha,\alpha}$-dibenzylglycine (Dbzg), and an orthogonally protected, tetrafunctional $C^{\alpha,\alpha}$-disubstituted analogue of aspartic acid Bcmg is described.

The preparation of amyloid fibril blocker peptides based on amyloid peptide hydrophobic core $A\beta_{16\text{-}20}$ is described. These blocker peptides containing sterically